REMARKS

A proper, single paragraph Abstract is submitted herewith.

The specification has been amended to correct obvious informalities, the corrections clearly not involving new matter.

The claims have been amended to correct informalities therein and claim 15 has been cancelled, thereby to obviate the 35 USC 112, second paragraph, rejections.

Claim 1 has been amended to exclude C_7-sulfonic acids. Support for this amendment is found in claim 13 as filed.

New claims 17-21 each contain subject matter that was deleted from claim 1 because recited therein in objectionable (indefinite) form. Similarly, claims 22 and 23 contain subject matter deleted from claim 4, claim 24 contains subject matter deleted from claim 5, claim 25 contains subject matter deleted from claim 7 and claims 26-30 contain subject matter deleted from claim 13.

Claims 1 and 13 have been amended to recite that the acid salt has a property of penetrating skin as defined by a flux of at least 2.34 $\mu g/cm^2 \cdot h$. Support for the 2.34 value is found in Fig. 4, Example 6, and higher values are found in Fig. 4, Examples 2-5, 7, 9 and 10.

The term "flux" is a technical term which is used for precise description of a controlled transepithelial (transdermal, transepidermal or transcutaneous) release rate of one or more pharmaceutically active substances from an application form which is intended to be applied to the skin. "Flux" specifies "permeated amount of active substance per area and time" (*i.e.*, $\mu g/cm^2$ x h).

The feature "flux" serves as a qualitative and quantitative measure of the permeation performance of transdermal administration forms. "Flux" could be determined in permeation experiments utilizing FRANZ type diffusion cells. For evaluation of the flux, cumulated amounts of permeated active substance are plotted against the corresponding time points. The course of release can be visualized by connecting the data points in the plot. Increase in the linear portion of the graph, dy/dx, is the permeation rate or flux respectively. It characterizes the constant diffusion rate. The experimental setup is known by those with ordinary skill in the art. Hence, those with ordinary skill in the art can definitely and reliably determine the "flux." A more detailed discussion of flux is in the literature, for

instance, by Sloan et al.: "Use of solubility parameters of drug and vehicle to predict flux through skin," J. Invest. Dermatol. 87, (1986), 244-252, a copy of which is appended hereto.

The rejections of claims 1, 4, 12, 13, 15 and 16 under 35 USC 102(b) as being anticipated by each of U.S. Patent No. 4,626,539 ('539) and U.S. Patent No. 4,879,297 ('297) and of claims 1-16 under 35 USC 103(a) as being unpatentable over '539 or '297 are respectfully but most strenuously traversed.

Both cited references, which are referred to in the specification, disclose tosylates. Tosylates are the salts of toluenesulfonic acid ($CH_3C_6H_4SO_2H$) which is in fact a C_7-sulfonic acid. Hence tosylates are not included in the definition of amended claim 1 due to omission of C_7-sulfonic acids. but d 4,6,23 has C_4-C_8 sulfonic a

Moreover, tosylates and naphthylates of morphines (disclosed in both cited references) are excepted from the subject matter of amended claim 1 by insertion of the recitation of a flux of at least 2.34 $\mu g/cm^2 \cdot h$. The flux of morphine salicylate and morphine tosylate are 0.95 and 1.56 $\mu g/cm^2 \cdot h$, respectively. These values are shown on a table appended hereto which is a copy of Fig. 4 to which have been added Comparison Examples 4-6 as well as "increase factors" with Comparison Example 4 as a baseline. where is it?

Hence, no claim is now anticipated.

As for the 35 USC 103(a) rejection, the following further arguments are presented.

It is an object of the present invention to provide salts of morphine derivatives which possess an improved skin permeability in relation to known acid addition salts of morphines. The permeability of a salt of a morphine derivative through skin has to be considered a characteristic feature of that particular substance. There is obviously no relation between the permeation behavior of salts of morphine derivatives and their molecular structure (molecular weight, pattern of substituents, electric or steric effects of substituents) or other physico-chemical properties (melting point, distribution coefficient, conductivity, polarity, pKs value and the like) of the respective acids as can be inferred from the examples. Accordingly, it can be seen that acid addition salts of a particular morphine with different acids possess a similar flux. Consequently, the permeation behavior of a salt of a morphine derivative is a characteristic feature of that particular substance and flux is a characteristic feature suitable to define the present invention.

No not similar from Fig 4

Quantitative comparative tests as requested in the international preliminary examination report were carried out and are presented in the appended table. For

technical reasons, it was not possible to use the same *in vitro* skin model for comparative tests as used for the initial tests. However, the skin permeation data obtained illustrate that both skin permeation test systems (nude guinea pig and bovine udder) are equivalent in respect to total amount of active agent penetrated through the skin and flux of active agents. The total amount of penetrated morphine base is 17.5 mg in case of guinea pig skin and 17.1 in case of cow's udder, whereas the flux is 0.45 $\mu g/cm^2 \cdot h$ in both cases.

The flux of morphine salicylate and morphine tosylate was determined to be 0.95 $\mu g/cm^2 \cdot h$ and 1.56 $\mu g/cm^2 \cdot h$, respectively, as stated above. This is an increase by a factor of 2 and 3.5, respectively, if compared to the flux of the free morphine base (Comparison Example 4). These data prove that these two acid addition salts possess a higher skin permeability than the free morphine base. But this is not true for any morphine salt. For instance, morphine propionate and morphine formiate (Comparison Examples 2 and 3, respectively), which were used for comparison in the original application, possess a flux similar to that of the morphine base.

Anyhow, the flux of those morphine salts being disclosed in the present application have to be compared to the flux of the free morphine base in order to appreciate inventiveness. The claimed minimum flux of 2.34 $\mu g/cm^2 \cdot h$ is 5X the

flux of the free morphine base and 2x and 3.5X the flux of morphine salicylate and morphine tosylate, respectively. This rebuts any *prima facie* obviousness.

It is known that morphines are substances which do not permeate the skin very well and require addition of permeation enhancing agents. Thus, the cited references disclose morphines for transdermal application which comprise different permeation enhancers such as large amounts of saturated or unsaturated fatty acids or fatty alcohols having 8 to 18 carbon atoms. No distinction is made in the cited references between the free base and a salt of a morphine derivative. Although a variety of morphine salts are disclosed in prior art, those skilled in the art have to conclude from the cited references that a satisfactory permeation of morphine salts through the skin cannot be achieved without addition of permeation enhancing agents. The cited references do not provide any hint or information indicating that certain morphine salts known in prior art or acid addition salts of morphines according to the present invention differ from the insufficient permeation behavior characteristic of morphines in general. Thus, it is submitted that the cited prior art does not even establish *prima facie* obviousness of the claimed invention.

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in excess of twenty. Also, charge any fee deficiency or credit any excess payment to the same deposit account.

In light of the foregoing, the application is now believed to be in proper form for allowance of all claims and notice to that effect is earnestly solicited. Please charge any fee deficiency or credit any excess payment to Deposit Account No. 10-1250.

Respectfully submitted,

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